REMARKS/ARGUMENTS

The Pending Claims

Claims 15-31 are currently pending, with claims 15-28 currently under examination, and claims 29-31 deemed withdrawn as directed to one or more nonelected inventions in response to the restriction requirement. Applicants request, upon the allowance of any elected product claim, the rejoinder and consideration of any nonelected method claims that are dependent on, or otherwise contain all of the limitations of, an allowed product claim.

Summary of the Office Action

The Office Action notes that a certified copy of the priority document has not been filed by Applicants.

The specification is objected to because it does not end in a period.

The declaration is objected to because of a non-initialed and non-dated handwritten correction to the declaration.

Claims 15-28 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description and enablement requirements.

Discussion of Priority Document

Applicants gratefully acknowledge the Office Action's notification that a certified copy of the priority document (i.e., DE 103 44 882.9) has not been lodged in the present application. A certified copy of the priority document is being obtained and will be submitted to the Office as soon as possible.

Discussion of Objections

The specification ends with the depiction of four chemical structures under the heading "Examples." Applicants respectfully submit that, since these chemical structures are not part of a sentence, a period would be inappropriate and could possibly cause confusion. Under the circumstances, Applicants request that the objection to the specification be withdrawn.

Applicants are in the process of preparing a corrected declaration, which will be separately submitted as soon as possible.

Discussion of the Written Description and Enablement Rejections

The Office Action rejects claims 15-28 as allegedly failing to comply with the written description and enablement requirements. In particular, the Office Action alleges as a basis for both the written description and enablement rejections that Applicants have failed to provide a method of making the compounds defined by pending claims 15-28. However, as discussed in detail below, one of ordinary skill in the art could have prepared the claimed compounds based on the information set forth in the present application in view of the state of the art at the time of the earliest possible priority for the present application, which is September 26, 2003.

In order to comply with the written description requirement of 35 U.S.C. § 112, first paragraph, it is sufficient that the specification "convey clearly to those skilled in the art the information that the applicant has invented the specific subject matter later claimed." See, e.g., *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.Q. 1976).

The enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation. See, e.g., *AK Steel Corp. v. Sollac*, 344 F.3d 1234,1244, 68 U.S.P.Q. 1280, 1287 (Fed. Cir. 2003). Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. See, e.g., *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q. 1400, 1404 (Fed. Cir. 1988).

The compounds defined by the pending claims are described in the specification of the present application. In particular, the pending claims recite a genus of compounds comprising a macrocyclic ring wherein the moieties A, U, G-E, V-W, X, Y, R^1, R^3, R^4, and R^9 are explicitly described in the specification, at, e.g., paragraphs 0003-0026.

As regards the so-called *Wands* factors, the quantity of experimentation necessary to make these compounds is relatively small in view of the clearly defined chemical structure of these claimed epothilone derivatives in the present application combined with the state of the prior art and the admittedly high skill level in the relevant art.

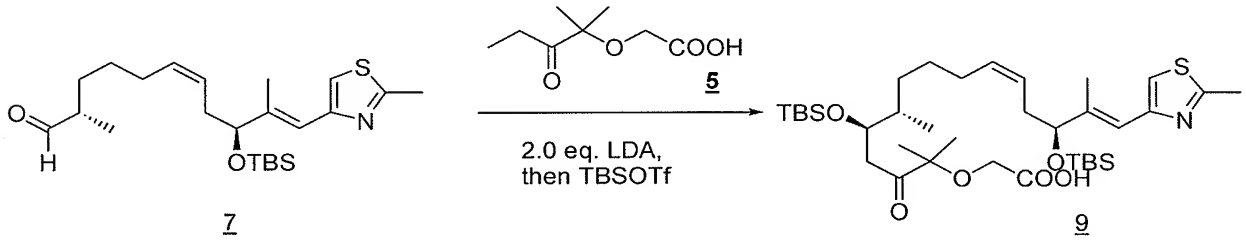
Indeed, as discussed in the concurrently submitted Rule 132 Declaration, the state of the art at the time of the earliest priority date available to the subject patent application, i.e., September 26, 2003, included knowledge of synthetic schemes that predictably provide for the preparation – without undue experimentation – of the compounds recited in the pending claims by merely providing appropriate starting materials, which would be readily known based on the desired final products disclosed in the present application and which were available by application of well-known synthetic methods, without requiring undue experimentation.

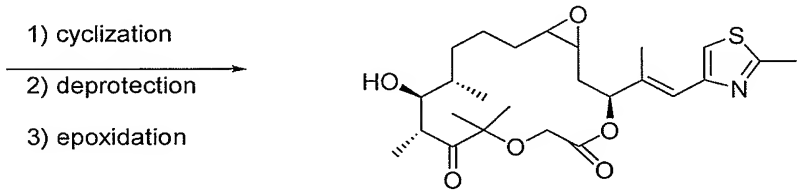
The Rule 132 Declaration points out that the synthesis of epothilones and derivatives thereof has been well known in the art, as evidenced, for example, by the recently published review article: Mulzer et al., *C.R. Chimie, 11:* 1336-1368 (2008). The Mulzer reference discloses numerous synthetic schemes that have been disclosed in much earlier references that predate the earliest priority date available to the subject patent application, i.e., September 26, 2003.

The Rule 132 Declaration describes two synthetic routes to epothilones that have been disclosed in the literature, which routes utilize different cyclization strategies to access the macrocyclic ring structures.

The first synthetic route, which is a synthesis pathway to epothilones A and C, was described in K.C. Nicolaou et al., *Angew. Chem., Int. Ed.* 35: 2399 (1996). Specifically, the Nicolaou reference teaches that aldehyde 7 reacts with the dianion derived from compound 8 to provide compound 9, which is then cyclized to form the macrolactone 10. Deprotection and epoxidation of 10 provides epothilone A (11). Substitution of compound 8 with an appropriate analog would be expected to provide the compounds of the present invention.

Thus, for example, the substitution of compound 8 in the synthesis shown in Scheme 1 of the Declaration with compound 5 predictably leads to the compounds of the present invention, wherein Y is O, as follows:

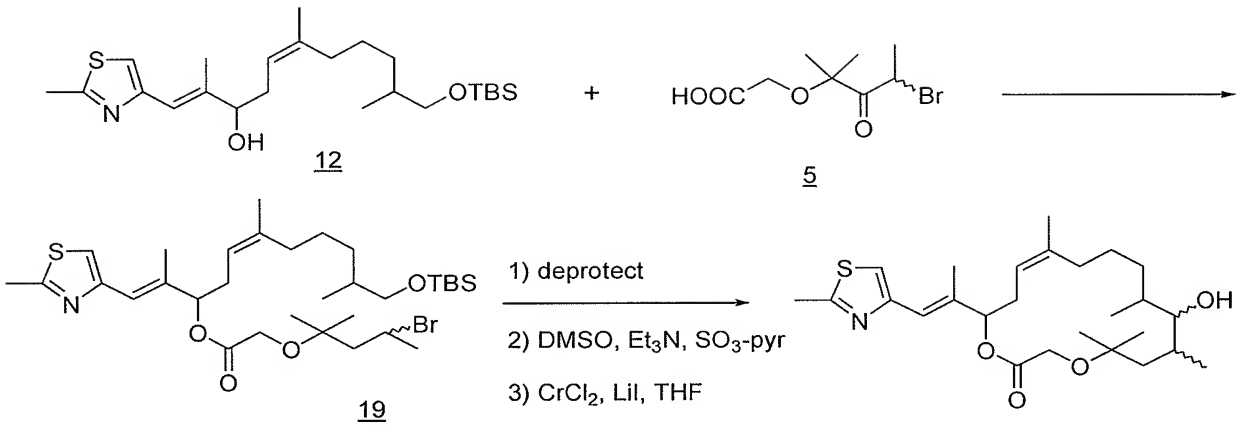




Similarly, executing the synthesis shown in Scheme 1 of the Rule 132 Declaration with substitution of compound 8 by compound 17, wherein R' is hydrogen, which is prepared by the method set forth in Scheme 4 of the Declaration, predictably leads to the compounds of the present invention wherein Y is NR^{10}.

The second synthetic route to epothilones and analogs thereof appears in U.S. Application Publication 2004/0082651 A1, which was published on April 29, 2004, based on International Patent Application No. PCT/EP01/11992, filed on October 16, 2001. The '651 publication teaches that compound 12 is esterified with compound 13 to provide ester 19. Deprotection of the TBS-protected alcohol in compound 12 followed by Swern oxidation of the alcohol to the corresponding aldehyde provides compound 20, which is cyclized under chromium Reformatsky conditions to provide deoxyepothilone compound 21. Substitution of compound 13 with an appropriate molecule provides the compounds of the present invention.

Thus, for example, substitution of compound 13 in the synthesis shown in Scheme 2 of the Declaration with compound 5 predictably leads to the compounds of the present invention wherein Y is O as follows:



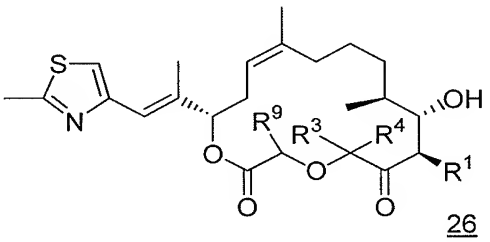
Similarly, executing the synthesis shown in Scheme 2 of the Rule 132 Declaration with substitution of compound 13 with compound 17, wherein R' is hydrogen, which is prepared by the method set forth in Scheme 5, predictably leads to the epothilone derivative wherein Y is NR^{10}.

The synthesis of compounds 5 and 17 is set forth in Schemes 4 and 5 of the Rule 132 Declaration. The Rule 132 Declaration attests that the reactions depicted in Schemes 4 and 5 were well known in the art before the earliest priority available to the subject patent application, i.e., September 26, 2003, thereby placing one of ordinary skill in the art in possession of compounds 5 and 17 before the aforesaid date.

Additional embodiments of the present invention, as recited in the pending claims, also were readily available to one of ordinary skill in the art before the earliest priority available to the subject patent application. For example, compound 7 from Scheme 1 and compound 12 from Scheme 2 are prepared by the method depicted in Scheme 3 of the Rule 132 Declaration. Substitution of heteroalkyl, heterocycloalkyl, heteroalkylcycloalkyl, heteroaryl, or heteroarylalkyl aldehydes for 2-methylthiazole-4-carboxyaldehyde 22 predictably leads to epothilone analogs having the recited moieties in place of the thiazole moiety found in naturally occurring epothilones. The aforesaid moieties correspond to groups A and U recited in the pending claims.

In addition, the reaction sequences set forth in Schemes 4 and 5 of the Rule 132 Declaration can be modified by substituting C_2-C_4 alkyl groups for the methyl groups in compound 1 of Scheme 4, or replacing compound 1 of Scheme 4 with cyclopropanone or

cyclobutanone, allowing for preparation of compound 26 wherein R^3 and R^4 are independently hydrogen or C_2-C_4 alkyl, or, taken together, R^3 and R^4 form a cycloalkyl group with 3 or 4 ring atoms. Substituting propyllithium, butyllithium, pentyllithium, cyclopropylmethyllithium, or cyclobutylmethyllithium for ethyllithium in Scheme 4 allows for preparation of compound 26 wherein R^1 is a C_1-C_4 alkyl group or a C_3-C_4 cycloalkyl group.



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Applicants submit that one of ordinary skill in the art was in possession of sufficient information provided by both the specification of the subject patent application and the technical literature at the relevant time, as evidenced by reaction schemes set forth in the Rule 132 Declaration, to practice the full scope of the invention as recited in the pending claims without undue experimentation. In view of the foregoing, the written description and enablement rejections of pending claims 15-28 are improper and should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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